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The conundrum of <2 cm pancreatic neuroendocrine tumors: a preoperative risk score to predict lymph node metastases and guide surgical management

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Abstract

Background: Management of <2 cm pancreatic neuroendocrine tumors (PanNETs) is controversial. Although often indolent, the oncologic heterogeneity of these tumors particularly related to lymph node (LN) metastases poses challenges when deciding between resection versus surveillance.

Methods: WE analyzed all patients who underwent resection of primary non-functional <2 cm with curative-intent at 8 institutions of the US Neuroendocrine Tumor Study Group from 2000–

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CONFLICTS OF INTEREST

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2016. PanNETs with poor-differentiation and Ki-67>20% were excluded. Our primary aim was to create a Lymph Node Risk Score (LNRS) that predicted LN metastases accurately for <2 cm PanNETs utilizing readily available preoperative data.

Results: Of 695 patients with resected PanNETs, 309 were <2 cm. Of these smal PanNETs , 25% were proximal (head/uncinate), 23% had a Ki-67≥3%, and only 8% were moderately-differentiated. Also, **only** 9% of all <2 cm PanNETs were LN(+); indeed lymph node positivity was associated with worse 5-year recurrence-free survival compared to LN(−) disease (80% vs 96%; p=0.007). Factors known preoperatively to be associated with LN metastases were proximal location (OR 4.0; p=0.002) and Ki-67≥3% (OR 2.7; p=0.05). Moderate-differentiation was not associated with LN(+) disease. Location and Ki-67 were assigned a value weighted by their odds ratio: (distal= 1, proximal= 4, and Ki-67<3%= 1and Ki-67≥3%=3), which formed a LNRS ranging from 1–7. Scores were categorized into low (1–2), intermediate (3–4), and high (5–7) risk groups. Incidence of LN metastases increased progressively based on risk group, with Low= 3.2%, Intermediate= 13.8%, and High= 20.5% (Table). Only 3.4% of PanNETs with a Ki-67<3% in the distal pancreas were LN(+) compared to 21.4% of PanNETs with a Ki-67≥3% in the head/uncinate.

Conclusion: This simple and novel LN risk score utilizes readily available preoperative factors (tumor location and Ki-67) to stratify risk of LN metastase accurately s for <2 cm PanNETs and may help guide management strategy.

INTRODUCTION

Pancreatic neuroendocrine tumors (PanNETs) are a rare and heterogeneous tumor type ,and currently represent about 3% of all pancreatic malignancies.[1] Although PanNETs are relatively indolent neoplasms, 5-year survival can be as great as 90–100% and as low as 25%.[2] Nearly 20% of PanNETs are considered to be “functional” tumors, manifesting with clinical signs and symptoms secondary to hormonal activation.[1,3] The large majority of PanNETs, however, are classified as “non-functional,” and thus either present late in their disease course due to tumor burden or are identified by chance.[2,3] As cross-sectional imaging increases in frequency and quality, non-functional PanNETs are being diagnosed at an increasingly small size.[4,5] The behavioral heterogeneity that distinguishes PanNETs has been noted even among PanNETs < 2 cm, with multiple studies reporting instances of nodal metastasis, distant metastasis, and disease recurrence among this group.[5–9] As a result, standardizing management, follow-up surveillance, and prognosis for these tumors remains a challenge.[10]

The sevenfold increase in the incidence of small PanNETs in the United States over the last two decades, as well as the uncertainty of their malignant potential, has created controversy over the optimal management of these neoplasms.[11,12] While operative resection remains the only cure for PanNETs,[10] several studies have proposed observation for tumors <2 cm as the preferred management strategy.[11–14] Yet, guidelines remain unclear, because both the European Neuroendocrine Tumor Society (ENETS) and the National Comprehensive Cancer Network (NCCN) offer several viable treatment strategies, including both resection and observation.[15,16] Without a definitive consensus, health care teams must utilize known

prognostic factors to predict tumor behavior and to help choose the appropriate approach for each individual patient.

While a number of poor prognostic factors have been implicated in the natural history of PanNETs, the impact of lymph node metastases on survival in non-functional PanNETs has been demonstrated clearly.[17–23] According to the American Joint Committee on Cancer, nodal disease automatically renders a Stage III diagnosis of Stage III disease in neuroendocrine tumors.[24] As such, even in the indolent group of <2 cm PanNETs, lymph node metastases may serve as a surrogate for aggressive tumor biology, which can aid in the decision to resect or observe the seneoplasms.

Given that only an average of 40% of all non-functional PanNETs have lymph node metastases, an accurate preoperative method for staging nodal status may be used to inform the surgical plan.[17] The aim of this study was to create a lymph node risk score (LNRS) that accurately predicts lymph node metastas accurately es for <2 cm non-functional PanNETs utilizing readily available preoperative data.

METHODS

Study Population

The U.S. Neuroendocrine Tumor Study Group (US-NETSG) is a collaboration of 8, high-volume institutions from across the United States, including Emory University, Michigan University, the Ohio State University, Stanford University, Vanderbilt University, Virginia Mason Clinic, Washington University in St. Louis, and University of Wisconsin. This database is comprised of all patients from these institutions with neuroendocrine tumors of the abdomen, specifically those located in the stomach, duodenum, ampulla, pancreas, liver, gallbladder, small bowel, appendix, colon, rectum, spleen, and peritoneum, who underwent operative resection from January 1, 2000 to December 31, 2016. For the purpose of this study, we included only patients with <2 cm, non-functional primary PanNETs who underwent curative-intent resection. Poorly differentiated and metastatic PanNETs , as well as those with a Ki-67>20% were excluded. All 30-day mortalities and R2 resections were also excluded. The primary end-point was presence of lymph node metastases, with the aim to create a preoperative Lymph Node Risk Score (LNRS) to predict accurately the presence of nodal metastases for <2 cm PanNETs.

Study Variables

Pertinent baseline demographic, preoperative, intraoperative, pathologic, and postoperative data were collected retrospectively through review of the medical records. Comorbidities were defined using the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) risk-calculator. Cancer staging was assigned per the guidelines of the American Joint Committee on Cancer 7th edition.[25] Neoadjuvant and adjuvant therapy, disease recurrence, and survival data were also collected. Approval by the Institutional review board was obtained at each institution prior to any data retrieval, and survival information was verified with the Social Security Death Index when appropriate.

Statistical Analyses

All statistical tests were executed using SPSS version 23.0 (Armonk New York Software, IBM Inc.) with statistical significance predefined as $p<0.05$. Descriptive and comparative analyses were performed for the entire cohort. Chi-squared analyses and Fisher's exact tests were used to compare categorical variables, and Student's t-test was used for continues variables, where indicated. Kaplan-Meier log-rank plots were calculated for recurrence-free survival (RFS), and univariable logistic regression was performed to evaluate both the clinicopathologic variables associated with lymph node positivity and the preoperative LNRS generated subsequently.

RESULTS

Patient Variables

Of 2,182 patients with neuroendocrine tumors in the US-NETSG database, 695 patients had low-to-intermediate, non-functional PanNETs who underwent curative-intent resection with a curative intent, 309 of which were <2 cm in size. Baseline demographics and clinicopathologic features of this study cohort are summarized in Table 1. Mean age was 58 years, 48% were male (n=147), and 76% (n=231) were Caucasian. Mean tumor size was 1.3 cm, and given that 75% (n=232) of tumors were located distally in the neck, body, or tail of the pancreas, only 25% (n=77) were located proximally in the head or uncinate. With regard to pathologic data, 93% (n=258) of tumors were well-differentiated, 77% (n=177) had a Ki-67 index <3%, and 9% (n=22) were lymph node-positive.

Recurrence-Free Survival Analysis:

Median follow-up was 35 months (IQR 13.9–59.1), and 13 patients (4%) experienced recurrence of disease after resection. Of those patients who developed a recurrence, , 6 recurred loco-regionally and 7 recurred distantly (1 in bone, 4 in liver, and 2 in lung). On Kaplan-Meier analysis, the 5-year RFS for patients with lymph node-positive disease was 80% compared to 96% for those with node-negative disease (p=0.007) (Figure 1). On univariable Cox regression, there was a 6-fold increase in risk of recurrence among patients with lymph node-positive versus negative disease (HR 5.9, 95% CI 1.4–25.3; p=0.016). Other pathologic factors, including final margin status, lymphovascular invasion, perineural invasion, tumor grade, and T-stage, were not associated with RFS in this cohort.

Lymph Node-Positivity and the Lymph Node Risk Score

Lymph node-positive patients when compared to those with lymph node-negative disease were more likely to have tumors located proximally in the pancreas (55% vs 23%; p=0.003), to have an advanced T-stage of T3/T4 (18% vs 3%; p=0.006), lymphovascular invasion (61% vs 8%; p<0.001), and perineural invasion (39% vs 12%; p=0.005) (Table 2). On binary logistic regression, proximal tumor location (OR 4.0, 95% CI 1.6–9.7; p=0.002), Ki-67 >3% (OR 2.7, 95% CI 1.0–7.2; p=0.054), positive margins (OR 3.3, 95% CI 1.0–11.0; p=0.052), lymphovascular invasion (OR 17.2, 95% CI 5.9–50.1; p<0.001), perineural invasion (OR 4.9, 95% CI 1.7–14.0; p=0.003), and advanced T-stage (OR 8.6, 95% CI 2.2–33.1; p=0.002) were all associated with an increased risk for lymph node-positivity (Table

3). When assessing lymph node-positivity simply by tumor location, 10 of the 193 (5.2%) distal tumors had lymph node4 positive disease compared to 12 of 67 (17.9%) proximal tumors (p<0.01).

The LNRS was created by assigning a value for the risk score based on the odds ratio on logistic regression for the preoperatively available factors of tumor location and Ki-67 index. For proximal tumor location, the OR was 4; thus, a score of 1 was given for distal tumor location and a score of 4 for proximal tumor location. For the Ki-67 index ≥3%, the OR was 2.7, so a score of 1 was given for a Ki-67 <3% and a score of 3 for a Ki-67 ≥3%. The final risk score ranged from 1–7, depending on the presence of one or both preoperative factors. The scores were then re-stratified into three groups, where a score of 1–2 corresponded with "low risk," a score of 3–4 with "intermediate risk," and a score of 5–7 with "high risk" for lymph node-positivity; 63%(n=195) of the cohort was classified as having a low LNRS, 20% (n=61) as having an intermediate LNRS, and 17% (n=53) as having a high LNRS. The incidence of lymph node-positivity ranged from 3% to 14% to 21% for a low, intermediate, and high LNRS, respectively (Table 4). Using binary logistic regression, an intermediate LNRS corresponded with a nearly 5-fold increase in risk for positive lymph nodes compared to a low LNRS (OR 4.9, 95% CI 1.5–15.7; p=0.007), while a high LNRS was associated with an almost 8-fold increase in risk for lymph node-positivity (OR 7.9, 95% CI 2.5–24.9; p<0.001) (Table 4). For patients with both a distally located tumor and a Ki-67 <3%, lymph node metastases occurred at a rate of 3%. Conversely, 21% of patients with tumors having both a proximal location and a Ki-67 ≥3% had node-positive disease.

DISCUSSION

Small pancreatic neuroendocrine tumors are a heterogeneous group of neoplasms with controversy regarding their best management. This study showed an association between lymph node metastases and decreased RFS among <2 cm, non-functional PanNETs. The preoperatively available factors of tumor location and Ki-67 index were utilized to create a simple and novel LNRSto stratify accurately these small tumors for risk of lymph node metastases. Indeed, using this LNRS ranging from1–7 based on the odds ratios on logistic regression for tumor location and Ki-67 index, <2 cm PanNETs were grouped into low (score 1–2), intermediate (score 3–4), and high (score 5–7) risk groups. The incidence of lymph node-positivity increased with increases in the LNRS, from 3% to 14% to 21%, respectively. Compared to low risk tumors, PanNETs classified as intermediate-risk were 5 times more likely to be lymph node-positive (OR 4.9; p=0.007), while high-risk PanNETs had a nearly 8-fold increase in lymph node metastases (OR 7.9; p<0.001).

Although the diagnosis of small, non-functional PanNETs has increased in the last few decades due in large part to the increase in cross-sectional imaging, current guidelines for the optimal management of these tumors remain ambiguous and not consistent.[11] ENETS recommends either surveillance or resection for <2 cm PanNETs, with careful weighing of the risks and benefits on a case-by-case basis.[16] Likewise, NCCN guidelines offer enucleation +/− regional lymphadenectomy, anatomic resection, and observation as viable management strategies.[15] Even the North American Neuroendocrine Tumor Society (NANETS) has an unclear consensus, suggesting enucleation or operative resection versus

observation depending on individual patient characteristics.[26] Findings in the literature have been conflicting as well. Although several studies, such as those of Lee *et al.*, and Sadot *et al.*, have concluded that it is safe to manage <2 cm PanNETs by observation,[11,13,27] others including Gratian *et al.*, and Haynes *et al.*, have suggested that these small tumors may still display an aggressive course.[6,9,12,28] Of course, with advances in functional imaging modalities such as DOTATATE, for example, the ability to preoperatively assess aggressive behavior via evaluation for lymph node metastasis may improve. In the current study, 9% (n=22) of patients had lymph node metastases at resection, and 13 recurred within a median follow-up of 35 months. Importantly, those patients with a high LNRS had a rate of lymph node metastases as great as 21%. These findings support the evidence that <2 cm PanNETs may manifest aggressive behavior, thus highlighting the need for both optimizing and standardizing their management.

When considering the characteristics of PanNETs that may predict poor outcomes and inform the decision to resect versus observe, there is substantial evidence supporting lymph node metastases as a marker of worse disease.[17,18,21,22] A study by Partelli *et al.*, demonstrated a 5-year disease-free survival of 70% for N1 disease versus 97% for N0 disease among patients with non-functional PanNETs.[17] Similarly, the study of Postlewait *et al.*'s showed that the 5-year RFS was 40% for patients with nodal metastasis compared with 85% in patients with lymph node-negative disease.[29] These findings are in accordance with the current study, because lymph node-positive patients in our cohort had a 5-year RFS of 80% compared to 96% for those who were lymph node-negative. Not only has lymph node metastasis in PanNETs been shown to correlate with decreased survival, but PanNETs specifically <3 cm metastasize at a rate as great as 33%.[30] Given this high incidence, the ability to predict nodal metastasis preoperatively in small PanNETs is of paramount importance and clinical relevance.

A number of clinicopathologic factors are correlated with lymph node-positivity in PanNETs, including tumor location in the head of the pancreas, increasing tumor size, lymphovascular invasion, and an increasedKi-67 index.[29,31,32] In the current study, although multiple factors were associated with an increased risk for lymph node metastasis, only tumor location and Ki-67 index were reliably available preoperatively. Hashim *et al.*, showed previously that PanNETs located proximally in the pancreas had a 2.8 times increase in risk for nodal disease compared to those in the body/tail.[31] In accordance with Hashim et al, our study demonstrated that proximal tumors had a 4-fold increase in risk for nodal metastases and that a Ki-67 index ≥3% had a nearly 3-fold increase in risk for nodal positivity. Because Ki-67 on preoperative biopsy has been found to correlate well with Ki-67 of the resected specimen, and because it is more sensitive than other clinicopathologic factors at predicting malignant behavior of neuroendocrine neoplasms, Ki-67 appears to be able to serve as a useful preoperative prognostic indicator.[33–35] Thus, tumor location and Ki-67 were combined to create a reliable LNRS from which to predict accurately the risk for lymph node metastasis among patients with <2cm PanNETs. Access to such information preoperatively may be used to guide and optimize patient management.

This study is limited by its retrospective design which may involve incomplete preoperative, pathologic, and survival data for the entire cohort. Specific limitations include incomplete

data on preoperative, radiographically measured tumor size, preoperative radiographically assessed lymph node status, and Ki-67 data based on the preoperative biopsy specimen. It is also limited by the small overall number of patients who ultimately had positive lymph nodes (n=22;9%) from which we based the Lymph Node Risk Score, however this low rate of lymph node-positive disease is an inherent characteristic of this cohort of patient with small <2cm pancreatic NETs. Furthermore, because only operatively resected neuroendocrine tumors were included in this database, those with worse tumor biology or worrisome features may have been selected. Nonetheless, this study is one of the largest cohorts of <2 cm PanNETs reported, and the use of 8, geographically diverse, academic institutions from across the U.S. eliminates single-institution bias.

In conclusion, a simple LNRSutilizing the readily available preoperative factors of tumor location and Ki-67 can stratify accurately the risk of lymph node metastases for <2 cm PanNETs. This risk score may be used to guide future treatment strategies by informing the decision to resect versus observe patients with small, non-functional PanNETs. This study demonstrated a rate of lymph node metastasis as great as 21% in patients with a high-riskLNRS. Ultimately, this LNRS may provide useful information to inform a meaningful conversation in the preoperative setting to determine the optimal management strategy for patients with <2cm PanNETs.

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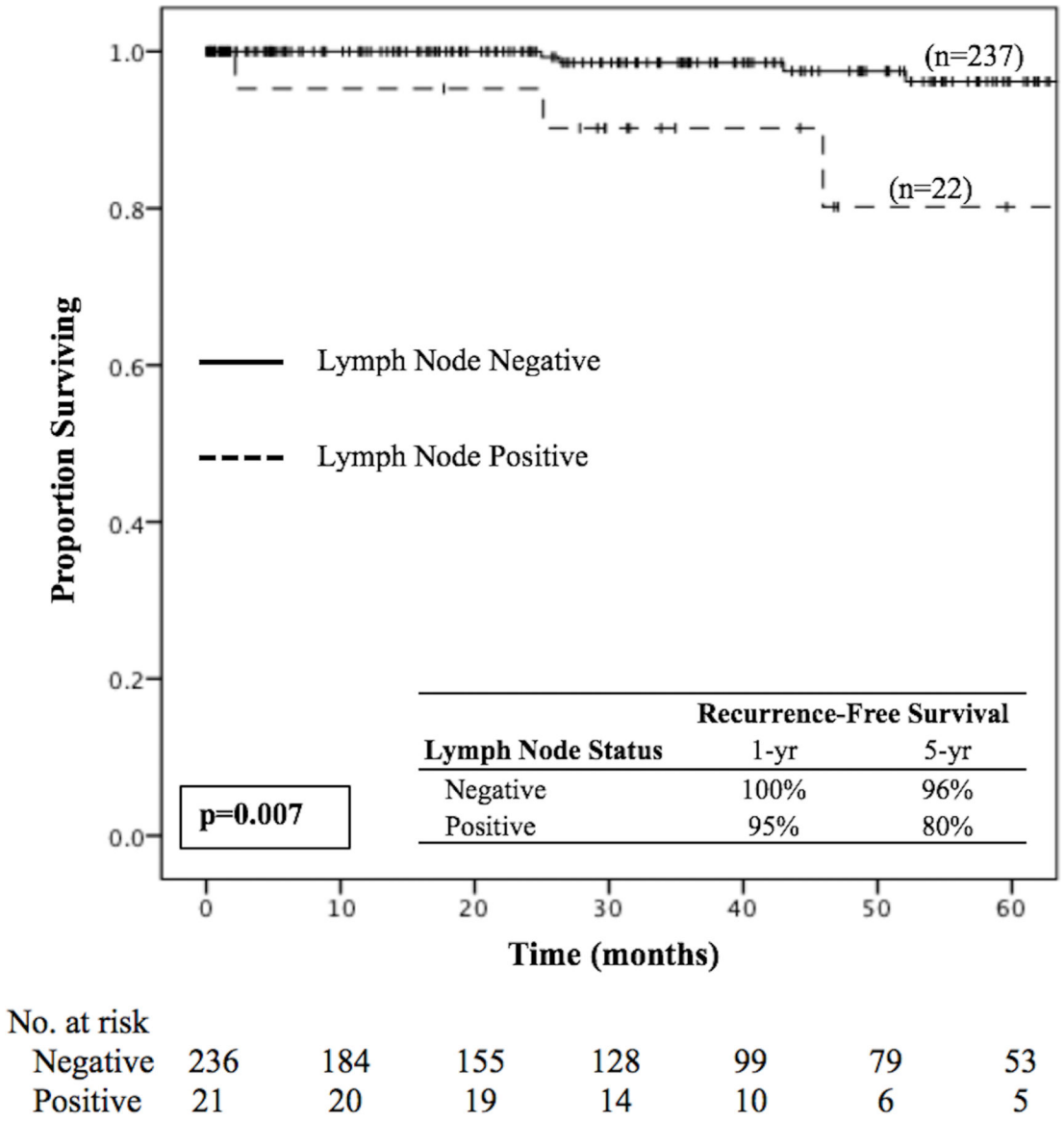

Figure 1.

Kaplan-Meier survival curve for recurrence-free survival in lymph node–positive versus lymph node–negative patients with <2 cm low/intermediate grade nonfunctional pancreatic neuroendocrine tumors.

Table 1.

Baseline Demographics and Clinicopathologic Variables of Patients with <2 cm Low/Intermediate Grade,Non-functional, Pancreatic Neuroendocrine Tumors (PNETs) from the US-NETSG Database who underwent Curative-intent Resection from 2000–2016 (n=309).

Baseline Variables	**n (%)**
Age (y), mean ± SD	58 ± 12
Male, n (%)	147 (48)
BMI, mean ± SD	29 ± 6
Comorbidities, n (%)[a]	
0	106 (34)
1	91 (29)
≥2	108 (35)
Race, n (%)	
White	231 (76)
Black	32 (11)
Other	40 (13)
ASA class, n (%)	
1	6 (2)
2	143 (47)
3	151 (50)
4	3
CgA (ng/L), mean ± SD	176 ± 332
Operative/ Pathologic Data	**n (%)**
Tumor Size (cm), mean ± SD	1.3 ± 0.4
Location of Tumor in Pancreas, n (%)	
Head/uncinate (Proximal)	77 (25)
Neck/body/tail (Distal)	232 (75)
OperativeTechnique, n (%)	
Open	198 (64)
Laparoscopic	70 (23)
Other	31 (13)
Type of Resection, n (%)	
Enucleation	28 (9)
Classic pancreatoduodenectomy	25 (8)
Pylorus preserving pancreatoduodenectomy	36 (12)
Central pancreatectomy	22 (7)

Baseline Variables	**n (%)**
Distal pancreatectomy	195 (63)
Total pancreatectomy	3 (1)
Tumor Differentiation, n (%)	
Well	258 (93)
Moderate	21 (8)
Ki-67 Index, n (%)	
< 3%	177 (77)
3–20%	52 (23)
Lymph Node-Positive, n (%)	22 (9)
Lymph Node Yield, median (IQR)	8 (3–13)
*ELSEVIER SEE BELOW Pancreatoduodenectomy	11 (7–17)
Distal Pancreatectomy	8 (4–12)
Enucleation/Central pancreatectomy	1 (1–2)
Post-operative Data	**n (%)**
Clavien-Dindo Classification, n (%)[b]	
I	48 (26)
II	67 (37)
IIIa	43 (23)
IIIb	11 (6)
IVa	11 (6)
IVb	3 (2)
Disease Recurrence	13 (4)
Region of Recurrence	
Locoregional	6 (46)
Locoregional + Distant	0 (0)
Distant	7 (54)
Deaths	11 (4)
Time to Death	
≤30 days	0 (0)
31–60 days	0 (0)
61–90 days	0 (0)
≥90 days	11 (100)

Abbreviations: SD, standard deviation; BMI, body mass index; ASA, American Society of Anesthesiologists; CgA, chromogranin A; IQR, interquartile range;

[a]Comorbidities are defined as any concurrent medical condition, including but not limited to, heart disease, chronic pulmonary disease, diabetes, renal disease, and liver disease as per the American College of Surgeons National Surgical Quality Improvement Program Risk Calculator.

[b] Clavien-Dindo is a grading scale for ranking the severity of post-operative complications ranging from I-V, where I represents the lowest acuity complication (one not requiring pharmacological treatment or surgical, endoscopic, or radiologic intervention), and V represents death.

[*] ELSEVIER THE THREE OPERATIVE PROCEDURES ARE IN A UNIQUE GROUP OF PATIENTS THAT NEEDS TOP BE DEFINED IN THE TABLE – I THINK THESE REPRESENT THE PATIENTS WITH LYMPH NODE-POSTITIVE DISEASE THIS NEEDS TO BE SPECIFIED BY THE AUTHORS

Table 2.

Distribution of Pathologic Factors among Patients with <2 cm Low/Intermediate Grade, Non-functional, PNETs from the US-NETSG Database who underwent Curative-intent Resection from 2000–2016, Stratified by Lymph Node-Positivity.

Pathologic Factors	Lymph Node Negative (n=287)	Lymph Node Positive (n=22)	p-value[a]
Location of Tumor in Pancreas, n (%)			0.003
Proximal	55 (23)	12 (55)	
Distal	183 (77)	10 (45)	
Tumor size			0.677
<1 cm	57 (24)	4 (18)	
1–1.5 cm	114 (48)	10 (46)	
≥1.5 cm	67 (28)	8 (36)	
AJCC T-Stage, n (%)			0.006
T1/T2	231 (97)	18 (82)	
T3/T4	6 (3)	4 (18)	
Tumor Differentiation, n (%)			0.646
Well	199 (92)	16 (89)	
Moderate	17 (8)	2 (11)	
Ki-67 Index, n (%)			0.090
<3%	136 (77)	10 (56)	
3–20%	41 (23)	8 (44)	
Mitotic Rate (per 10 HPF), n (%)			0.081
<2	141 (92)	9 (75)	
2–20	12 (8)	3 (25)	
Final Resection Status, n (%)			0.065
R0[b]	222 (94)	18 (82)	
R1[b]	15 (6)	4 (18)	
Lymphovascular Invasion, n (%)			<0.001
Negative	186 (92)	7 (39)	
Positive	17 (8)	11 (61)	
Perineural Invasion, n (%)			0.005
Negative	161 (88)	11 (61)	
Positive	21 (12)	7 (39)	

Abbreviations: AJCC, American Joint Committee on Cancer; HPF, high power fields;

[a] Statistical significance is indicated by a p<0.05.

[b] R0 resection refers to negative margins on pathologic review of the specimen, while R1 resection refers to positive margins on pathologic review of the specimen.

Table 3.

Association of Pathologic Factors with Risk for Lymph Node Positivity in Patients with <2 cm Low/Intermediate Grade, Non-functional, PNETs from the US-NETSG Database who underwent Curative-intent Resection from 2000–2016.

	Logistic Regression Lymph Node Positivity	
Pathologic Factors	**OR (95% CI)**	**p-value[a]**
Tumor Location in Pancreas		
Distal	**Ref**	**--**
Proximal	**4.0 (1.6–9.7)**	**0.002**
Tumor Size		
<1 cm	Ref	--
1–1.5 cm	1.25 (0.4–4.2)	0.716
≥1.5 cm	1.7 (0.5–5.9)	0.405
Tumor Differentiation		
Well	Ref	--
Moderate	1.5 (0.3–6.9)	0.631
Ki-67 Index		
<3%	**Ref**	**--**
3–20%	**2.7 (1.0–7.2)**	**0.054**
Final Resection Status		
R0	Ref	--
R1	3.3 (1.0–11.0)	0.052
Mitotic Rate (per 10 HPF)		
<2	Ref	--
2–20	3.9 (0.9–16.4)	0.062
Lymphovascular Invasion		
Negative	Ref	--
Positive	17.2 (5.9–50.1)	<0.001
Perineural Invasion		
Negative	Ref	--
Positive	4.9 (1.7–14.0)	0.003
Advanced T Stage		
T1/T2	Ref	--
T3	8.6 (2.2–33.1)	0.002

Abbreviations: OR, odds ratio; CI, confidence interval; HPF, high power fields;

[a]Statistical significance is indicated by a p<0.05.

Bold values indicate preoperatively measurable variables through imaging or biopsy.

Table 4.

Rate and Risk of Lymph Node-Positivity According to the Preoperative Lymph Node Risk Score among Patients with <2 cm, Low/Intermediate Grade, Non-functional ,PNETs from the US-NETSG Database who underwent Curative-intent Resection from 2000–2016.

	Lymph Node Positivity*			
	Incidence	**p-value†**	**OR (95% CI)**	**p-value†**
Lymph Node Risk Score		<0.001		
Low (Score 1–2) (n=195)	3%		Ref	--
Intermediate (Score 3–4) (n=61)	14%		4.9 (1.5–15.7)	0.007
High (Score 5–7) (n=53)	21%		7.9 (2.5–24.9)	<0.001

Abbreviations: OR, odds ratio; CI, confidence interval;

*Chi-squared analysis was used to compare incidence of lymph node positivity among the risk groups, while binary logistic regression was used to evaluate risk for nodal disease based on the assigned lymph node risk score.

†Statistical significance is indicated by a p<0.05.